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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/275,883	03/25/99	RENNER	W	1700.0020001

HM22/0815
STERNE KESSLER GOLDSTEIN & FOX
1100 NEW YORK AVE NW
SUITE 600
WASHINGTON DC 20005-3934

EXAMINER	
SCHNIZER,R	
ART UNIT	**PAPER NUMBER**
1632	11

DATE MAILED: 08/15/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary	Application No. 09/275,883	Applicant(s) Renner et al
	Examiner Richard Schnizer	Group Art Unit 1632

☒ Responsive to communication(s) filed on *May 30, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-34, 38-70, and 74* is/are pending in the applicat

Of the above, claim(s) *5 and 7* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4, 6, 8-34, 38-70, and 74* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3,6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Election/Restriction

Applicants' election with traverse of group I in Paper No. 10 is acknowledged. In a telephone conversation with Stephen Whiteside on 7/27/00, the species human erythropoietin was elected with traverse.

The traversal is on the ground(s) that there is no undue search burden because a search of the claims of group I would provide useful information for examination of the claims of group II, thus the searches would be overlapping. This is not found persuasive because, while the searches might overlap, they are not coextensive. That is, examination of group II in a addition to group I would require a further search of non-overlapping material, which would constitute a serious burden.

The requirement is still deemed proper and is therefore made FINAL. Claims 5 and 7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claims 1-4, 6, 8-34, 38-70, and 74 are in consideration in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1-4, 6, 8-14, 16-34, 38-70, and 74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64 Number 244, pp. 71427-71440 (also available at www.uspto.gov).

The claimed invention encompasses the genus of open reading frames encoding a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species has been described by complete structure. In this case, Applicant describes only a single species, comprised by SEQ ID NO: 1, by complete structure. Next, it is determined whether a representative number of species has been described by other relevant identifying characteristics. The specification describes the characteristics required to

qualify as a member of the claimed genus, as well as methods which one might employ in order to isolate a member of the genus, however it describes no single species which comprises all of the characteristics required, other than SEQ ID NO:1. This disclosure is not deemed sufficient to reasonably convey to one skilled in the art that applicant was in possession of the more than a single species of the claimed genus at the time of filing, and the written description requirement is not satisfied.

Enablement

Claims 1-4, 6, 8-34, 38-70, and 74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use in BHK-21 cells *in vitro* of nucleic acid molecules encoding a heterologous open reading frame and a Sindbis virus non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase with P726S nsP2 and G153E nsP4 mutations, wherein the heterologous open reading frame is operatively linked to a promoter recognized by Sindbis virus RNA-dependent RNA polymerase, does not reasonably provide enablement for the use of these nucleic acids in any other cell type *in vivo* or *in vitro*, or for the use of any other nucleic acid which lacks a promoter recognized by Sindbis virus RNA-dependent RNA polymerase, or which encodes any other non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase, in any cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The invention encompasses nucleic acid molecules encoding a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase and methods of using the nucleic acids. The molecules also encode an open reading frame which must undergo at least one RNA-dependent RNA polymerase-mediated replication event in order to be translatable. Claims 32-34 and 68-70 are specifically directed to pharmaceutical compositions comprising a nucleic acid as the active ingredient. For the purpose of examination under 35 U.S.C. 112, first paragraph, pharmaceutical compositions must be enabled for therapeutic use. Thus claims 32-34 and 68-70 are drawn specifically to gene therapy, particularly in light of the specification at page 1, lines 17-19, and pages 33-37. Claims 25-31 and 61-67 are drawn to the use of the nucleic acids of the invention in humans, and have no asserted utility other than gene therapy. Because the specification asserts a use for the claimed nucleic acid molecules in gene therapy, all of the claims, when read in light of the specification, read on gene therapy. The asserted utilities of the invention also encompass the construction of transgenic animals comprising the claimed nucleic acids, and the expression of RNAs and polypeptides in cultured cells.

Applicant provides working examples of several Sindbis virus-based expression vectors comprising a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase, and any one of several different heterologous ORFs which require at least one RNA polymerase replication event prior to expression. The encoded polymerase comprises a P726S nsP2 mutation in combination with a G153E nsP4 mutation. Mutation P726S in nsP2 allows non-cytopathic function of the polymerase in BHK-21 cells, whereas expression of the wild type polymerase leads

to cell death. Mutation G153E in nsP4 confers temperature-sensitivity on the polymerase, causing it to be essentially inactive at temperatures above 34°C. See paragraph bridging pages 21 and 22; page 22, lines 17 and 18; and page 23, lines 22-24. Using the nucleic acids of the invention, Applicant discloses expression of several heterologous proteins in BHK-21 cells, and green fluorescent protein is expressed in cultured human foreskin fibroblasts. However, Applicant fails to teach any other example of a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase, or any polymerase template which lacks a promoter recognized by Sindbis virus RNA-dependent RNA polymerase. In Genentech Inc. v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See , e.g. , Hybritech Inc. v. Monoclonal Antibodies, Inc. , 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

Disclosure of a single polynucleotide encoding one non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase, and one promoter recognized by that polymerase, is enabling only for that particular polynucleotide and degenerate ones encoding the same polymerase.

With respect to the issue of host cell range, Agapov et al have set forth the state of the art in the use of DNA molecules encoding non-cytopathic RNA-dependent RNA polymerases and heterologous open reading frames. See Proc. Nat. Acad. Sci. USA 95: 12989-12994, 10/1998. Sindbis virus-based vectors comprising a mutation at position 726 of nsP2 were used to express heterologous proteins in cultured cells. While RNA replication was obtained in BHK-21 and CHO cells, and to a lesser extent in Vero cells, replication was not observed in any other cell type tested, including primary chicken fibroblasts, MDBK, MDCK, 293, HeLa, and PC12 cells. All of these cells support RNA replication by cytopathic polymerases, and the reason why replication by non-cytopathic polymerases is not supported is unknown. Agapov concludes that the unknown obstacles to replication must be overcome before host range can be increased, and particularly before any *in vivo* applications of expression vectors encoding non-cytopathic RNA-dependent RNA polymerases can be implemented. See page 12994, column 1, first full paragraph.

The limited host range caused by mutation to nsP2 was unexpected in view of previous results with cytopathic polymerases. In this context, it is important to note that the effects of temperature-sensitive mutations in the RNA polymerase, particularly in combination with a mutation at position 726, are unknown and unpredictable. It is pointed out, that although Applicant used the DNA molecule of the invention to express GFP in cultured human foreskin fibroblasts, no evidence was presented indicating that the RNA-dependent RNA polymerase was non-cytopathic in these cells. Because Applicant provides evidence of non-cytopathic polymerase function in only one cell line *in vitro* (BHK-21 cells), it is reasonable to limit the scope of the

invention to use in that cell line. In the event that Applicant is able to show that the invention will function *in vivo*, the following considerations regarding therapeutic use will still apply.

At the time the invention was made, successful implementation of therapeutic protocols based on administration of nucleic acids was not routinely obtainable by those skilled in the art. This is reflected by two recently published reviews on gene therapy. Verma et al (1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concludes, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). While Applicant's invention addresses the issue of regulatable gene expression, no evidence is presented which would convey to one of skill in the art that the art-recognized problems with sustainable gene expression have been overcome. Furthermore, the issue of delivery looms large in view of the results of Agapov which indicate that vectors closely related to those of the instant invention must be modified in as yet unknown ways before they can be expected to function *in vivo*.

Because Applicant discloses only a single Sindbis virus temperature-sensitive, non-cytopathic RNA-dependent RNA polymerase which cannot be expected to function in a non-cytopathic manner in cells other than BHK-21, because Applicant has disclosed only a single

promoter which is recognized by any temperature-sensitive, non-cytopathic RNA-dependent RNA polymerase, and because Applicant has failed to overcome the art-recognized difficulties associated with gene therapy, one of skill in the art would have to perform undue experimentation in order to practice the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 16-19, 21, 22, 41, and 52-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 41 are indefinite because the specification fails to unambiguously define the term "undetectable". This term is defined with respect to expression of genes transcribed by RNA-dependent RNA polymerase. See page 15, lines 22-26. However this definition varies with the assay used to detect the protein which is being expressed. Several assays are recommended for use, including a fluorescence assay, an activity assay, and an immunological assay. Each of these can reasonably be expected to have a different sensitivity, thus the definition of "undetectable" varies with the assay. If an immunological assay and an activity assay were applied to measure the expression of erythropoietin, and thereby infer RNA polymerase activity, on which assay would one rely in order to determine the metes and bounds of the invention?

Claim 16-19, 21, 22, 52-55, 57, and 58 are incomplete because they lack a critical method step. The claims recite no step at which the polypeptide or RNA is expressed.

Claims 20 and 56 are incomplete because they lacks critical a method step. The claims recite no step at which alphaviral particles are produced.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached on Mondays and Thursdays between the hours of 6:20 AM and 3:50 PM, and on Tuesdays, Wednesdays and Fridays between the hours of 7:00 AM and 4:30 PM (Eastern time). The examiner is off every other Friday, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton, can be reached at 703-308-2801. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Richard Schnizer, Ph. D.

Karen M. Hauda

KAREN HAUDA
PRIMARY EXAMINER